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Customer No. 31013 Atty Docket No. 056001/02822

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Murphy et al.	
Serial No.	:	09/523,809	Confirmation No. 6553
Art Unit	:	1636	
Filed	:	March 13, 2000	
Examiner	:	S. Kaushal	
For:		**BIOENGINEERED TISSUE CONSTRUCTS AND METHODS FOR PRODUCING AND USING THEREOF**	

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited on December 16, 2005, with the United States Postal Service as First Class Mail in an envelope addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Signature: Silvia Salvadori

Silvia Salvadori, Reg. No. 48,265
Kramer Levin Naftalis & Frankel LLP

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION OF KATHERINE C. FARIA

I, Katherine C. Faria, Director of Process Engineering at Organogenesis Inc. declare as follows:

1. I am a citizen of the United States of America and currently reside in Middleboro, Massachusetts, U.S.A.

2. I received a Bachelor of Science degree in Biology with a minor in Chemistry in 1993 from University of Massachusetts Dartmouth in Dartmouth, Massachusetts.

3. For over 11 years, I have been engaged in the practice of cell culture. For 7 years, since 1998, with the exception of a 9-month period in 2002, I have been, and currently

am, employed at Organogenesis Inc., 150 Dan Road, Canton, MA 02021-2820, in the Process Development department with duties related to culture of human dermal fibroblasts, human epidermal cells; organotypic culture of both single and bi-layer tissue constructs of skin; and media development for these cell cultures and organotypic cell cultures.

4. I have reviewed the above-referenced U.S.S.N. 09/523,809 (the '809 application), including the pending claims, and I am familiar with the subject matter disclosed and claimed therein.

5. I have reviewed the Office Action mailed June 16, 2005 ("Office Action"), and made this declaration in support of the concurrently filed *Response to Office Action.*

6. I understand from reviewing the '809 application that the presently claimed invention is directed to cultured skin constructs having at least two layers of cells, comprising a first layer of fibroblast cells producing an extracellular matrix layer in the absence of both exogenous matrix components and a mesh member during the culturing conditions and a second layer of epithelial cells disposed on the first cell layer. The second layer may form an epidermal cell layer when the selected epithelial cells are keratinocytes. The presently claimed invention is also directed to methods of making and using the skin construct.

7. I understand that in the Office Action, claims 31-71 were rejected for failing to comply with the "enablement" requirement of 35 U.S.C. § 112, ¶ 1.

8. I have been informed by the attorneys for the '809 application ("Applicants' attorneys") that the standard for determining whether the specification meets the enablement requirement of 35 U.S.C. § 112, ¶ 1 is whether the experimentation needed to practice the claimed invention is undue.

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9. I have been informed by Applicants' attorneys that one of ordinary skill in the art would be an individual with an undergraduate degree in cell biology and at least two years of postgraduate research or work experience in the field of tissue constructs. Thus, in my opinion, one of ordinary skill in the art, when reviewing of the teachings of the '809 application, would know how to prepare a layer of dermal fibroblast cells that produce an extracellular matrix having such natural byproducts such as type I and type III collagen, decorin, fibronectin, tenascin, glycosaminoglycans, etc. One of ordinary skill in the art would further know which culture media may be used to prepare such a layer.

10. As such, it is my opinion that one of ordinary skill in the art would understand based on '809 application how to prepare without undue experimentation a cultured skin construct with at least two layers comprising cultured fibroblasts which synthesize, assemble and produce a layer of extracellular matrix in the absence of both exogenous matrix components and a mesh member during the culturing conditions, and a second layer of epidermal cells which may form an epidermal cell layer when the selected epithelial cells are keratinocytes.

11. The reasons for my conclusion in the preceding paragraph are simple. It is well known in the art what culture media may be used to obtain a layer of dermal fibroblasts or epidermal cell layers producing their natural byproducts. For example, it is well known in the art that dermal fibroblast cells naturally produce type I and type III collagen and other byproducts The '809 application correctly confirms this conclusion (*see, e.g.*, Specification page 3, lines 19-23, page 4, line 1, to page 5 line 2, page 5 line 26, to page 6 line 5, page 7 lines 20-27, page 8, lines 20-29, etc.).

12. It is also well known in the art how to form an epidermal cell layer from keratinocyte cells, which are naturally found in such epidermal cell layers. The '809 application confirms this conclusion by incorporating by reference a number of references that teach such

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methods (*see, e.g.*, Specification page 19, lines 18-22, citing U.S. Patent Nos. 5,712,163 and 5,536,656 and page 21, lines 5-6 citing U.S. Patent No. 5,374,515).

13. It is further well known in the art what culture media to use to grow a layer of dermal fibroblast cells or epidermal cell layers to produce their natural byproducts. Again, the '809 application confirms this well known knowledge by incorporating by reference a number of teachings of such culture media (*see, e.g.*, Specification page 12, line 29 to page 13 line 9).

14. However nothing in the state of the art as of the earliest claimed filing date which I understand is November 19, 1998 teaches, discloses or even suggests that such a tissue construct could be prepared without an external mesh member. For example, U.S. Patent Nos. 5,580,781, 5,443,950, 5,266,480, 5,032,508, 4,963,489, etc., all confirm the reliance on synthetic or mesh members for producing the tissue construct (*see, e.g.*, Specification page 10, lines 21-29).

15. On the other hand, the '809 application itself discloses how to prepare the tissue constructs of the invention.

16. For example, the '809 application discloses how to grow fibroblast cells. The '809 application discloses, *inter alia*, which media to use and which supplements to add such as amino acids, growth factors and hormones (*see, e.g.*, Specification page 11, line 11, to page 14 line 8, page 14, line 16, to page 16 line 19 and Examples 1, 3, 5, 6, 9-11, 15, 17).

17. Additionally, the '809 application discloses how to prepare a layer of extracellular matrix from dermal fibroblast cells in the absence of exogenous matrix components. For example, the '809 specification teaches to supplement the culture media with components that assist in matrix synthesis, secretion or organization when the matrix-producing cells become

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confluent (*see, e.g.*, Specification page 17, lines 7-28, page 18, line 7 to page 19 line 6, page 23, line 26, to page 24, line 6, and Examples 1, 3, 5, 6, 9-11, 15, 17).

18. Furthermore, the '809 application discloses, *inter alia*, how to prepare a layer of epidermal cells. For examples, the '809 specification teaches the density of the epithelial cells to seed to the top-surface of the cell-matrix constructs to form the tissue construct of the claimed invention (*see, e.g.*, Specification page 19, lines 26, to page 20 line 12).

19. Thus, as set forth above, the '809 application is enabling for the preparation of a layer of human fibroblast cells that produce an extracellular matrix in the absence of exogenous matrix components and for growing epidermal cells. Accordingly, it is my opinion that the '809 application provides ample guidance for practicing the claimed invention.

20. Armed with this knowledge of how to practice the cell culture conditions for which the state of the technology is well known in the art, how to prepare a layer of extracellular matrix from dermal fibroblast cells in the absence of exogenous matrix components and how to grow human fibroblasts and epidermal cells, one of ordinary skill in the art would understand how to practice the claimed invention. Experimentation, if any is needed, would be routine at most, and certainly would not be undue.

21. Therefore, it is my opinion that one skilled in the art would be able to practice the invention of claims 31-71 without undue experimentation since the '809 application provides ample teachings to prepare a cultured skin construct with at least two layers comprising cultured fibroblast cells which synthesize, assemble and produce a layer of extracellular matrix in the absence of both exogenous matrix components and a mesh member during the culturing conditions, and a second layer of epithelial cells disposed on the first cell layer.

I HEREBY DECLARE that all statements made of my own knowledge are true, and all statements made on information and belief are believed to be true. I make this

declaration understanding that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001) and may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Date: December 16, 2005 By: 12/16/05

Katherine C. Faria